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Maps of end-stage renal disease and amounts of angiotensin-converting enzyme inhibitors prescribed in Japan

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Background. We recently found regional differences in the incidence of end-stage renal disease (ESRD) in Japan, which is generally ethnically homogeneous, suggesting that factors other than genetic may contribute to the difference. Here, we examined regional differences in the amounts of expenses spent on antihypertensives, especially angiotensin-converting enzyme (ACE) inhibitors, in our search for an explanation.

Methods. Annually, the Japanese Society for Dialysis Therapy reports the numbers of patients entering maintenance dialysis in each prefecture of Japan since 1982. We used the findings for 1995 to 2000 to calculate the annual incidence of ESRD in each of the 11 regions of Japan. In addition, regional differences in annual amounts paid for antihypertensive drugs, presumably corresponding to the amounts used, during the same 6 years, corrected for population, were estimated.

Results. As in our 1982 to 1998 study, the incidence of ESRD was high in Okinawa, Kyushu, and Shikoku, while low in Hokuriku, Koshinetsu, and Tohoku ($P < 0.0001$) [one-way repeated measures analysis of variance (ANOVA)]. We found regional differences in the corrected sum paid for total antihypertensive drugs, ACE inhibitors and calcium antagonists. Only ACE inhibitors were negatively correlated with the incidence of ESRD by linear and multiple regression analyses.

Conclusion. The renal protective effects of ACE inhibitors have been established by results with animal models of progressive nephropathy and large-scale clinical trials. Our epidemiologic results for Japan as a whole show the same protective effects still more convincingly from a different approach.

We earlier reported regional differences within Japan in the incidence of patients with end-stage renal disease (ESRD) starting maintenance dialysis therapy [1, 2]. Because this country, generally speaking, is racially homogeneous, we believe there may be factors other than genetic that contribute to the difference. Our aim was to identify such factors. Strict blood pressure control [3, 4], especially with angiotensin-converting enzyme (ACE) inhibitors [5–10], is now the major treatment strategy available at present in arresting renal failure.

Therefore, when we set out to identify factors related to the regional differences, we decided to examine the amounts of money spent for antihypertensives, especially those paid for ACE inhibitors, in these different regions within Japan.

Key words: regional difference, end-stage renal disease, chronic renal failure, incidence, risk factor, angiotensin-converting enzyme inhibitors, antihypertensive therapy, prevention.

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METHODS

The annual amount of money paid for antihypertensive drugs prescribed in each of 47 prefectures of Japan has been compiled by Crecon Research & Consulting, Inc. (Tokyo, Japan) and is known only for the recent 6 years between 1995 and 2000. For that reason, we analyzed the annual incidence of ESRD for the prefectures for the same 6 years starting in 1995. As in our earlier study [1], the numbers of patients with ESRD entering maintenance dialysis therapy, either hemodialysis or peritoneal dialysis, were obtained from reports of the Japanese Society for Dialysis Therapy [11]. The method of calculation was as previously reported [1]. In brief, for each of the 11 regions of Japan (see below), we calculated annual means (per population of one million) for the 6 years of the study from 1995 to 2000. This mean was the average for that region of the number of patients with ESRD entering dialysis, corrected for population, every year during the 6 years.

Definition of the 11 regions

The 47 prefectures of Japan have been traditionally divided into 11 regions with generally homogeneous cultural and socioeconomic activities that differ somewhat between regions. Details of the division vary slightly; our definition is previously described [1] as region 1,

Table 1. Regional differences in annual incidence of end-stage renal disease (ESRD) and usage of antihypertensive agents

Region	ESRD incidence[a] *million/year*	Usage of antihypertensive agents *yen/person/year*			Age[a] *years*	Aged[a] population %
		Total[a]	ACE inhibitors[a]	Calcium antagonists[a]		
1, Hokkaido	250 ± 8	5670 ± 130	1330 ± 20	2660 ± 50	62.6 ± 0.5	16.4 ± 0.5
2, Tohoku	216 ± 6	5790 ± 100	1530 ± 30	2760 ± 40	63.0 ± 0.2	19.2 ± 0.4
3, Kanto	224 ± 5	4150 ± 100	1020 ± 20	2030 ± 50	61.6 ± 0.2	14.2 ± 0.3
4, Koshinetsu	212 ± 10	5010 ± 100	1230 ± 20	2470 ± 60	63.4 ± 0.3	19.6 ± 0.3
5, Hokuriku	210 ± 5	4710 ± 100	1130 ± 10	2390 ± 50	62.7 ± 0.4	18.7 ± 0.3
6, Tokai	232 ± 4	4270 ± 70	1080 ± 10	2090 ± 30	62.3 ± 0.2	16.0 ± 0.4
7, Kinki	238 ± 5	4190 ± 70	1010 ± 10	2080 ± 40	62.8 ± 0.2	15.8 ± 0.4
8, Chyugoku	225 ± 6	4600 ± 80	1120 ± 20	2330 ± 40	63.6 ± 0.3	20.2 ± 0.4
9, Shikoku	261 ± 6	4920 ± 100	1160 ± 20	2470 ± 50	62.6 ± 0.3	20.7 ± 0.3
10, Kyushu	264 ± 6	4440 ± 80	1040 ± 10	2310 ± 40	63.4 ± 0.2	19.3 ± 0.3
11, Okinawa	274 ± 10	2980 ± 140	730 ± 20	1460 ± 80	60.1 ± 0.3	12.9 ± 0.4

ACE is angiotensin-converting enzyme. Mean ± SEM.
[a]$P < 0.0001$ by ANOVA

Hokkaido; region 2, Tohoku; region 3, Kanto; region 4, Koshinetsu; region 5, Hokuriku; region 6, Tokai; region 7, Kinki; region 8, Chyugoku; region 9, Shikoku; region 10, Kyushu; and region 11, Okinawa. Incorporation of data based on the prefecture into larger units based on the region should decrease error due to the influx and efflux of population that occur across prefectural lines but that are mostly restricted within a given region.

Possible factors for regional differences in ESRD

We examined some factors that might contribute to regional differences in ESRD dynamics. Annual values for the years from 1995 to 2000 were calculated for each region from those based on prefectures: the amounts of money paid for all kinds of prescribed antihypertensive drugs, ACE inhibitors, and calcium-antagonists, all corrected for population, the mean age of patients with ESRD entering dialysis therapy [11], and the percentage of people 65 years old or older [12]. The amount paid for antihypertensive drugs prescribed in each of the 47 prefectures, reported as the annual sales of the major classes of antihypertensive products by prefecture at the reimbursed price level (Crecon Research & Consulting, Inc.), was corrected for population and used to calculate the amounts paid in the different regions.

Statistical analysis

One-way repeated measures analysis of variance (ANOVA) was used to compare the incidence of ESRD and other factors among the different regions. Linear as well as multiple (stepwise forward) regression analyses were applied to identify independent factors for the regional differences in the incidence of ESRD. All numeric results are given as means ± SEM, and the level of $P < 0.05$ and $F > 4.0$ were considered to be statistically significant.

RESULTS

Annual ESRD incidence

Since the annual usage of antihypertensive drugs, in money basis, in each prefecture was reported only in 6 years from 1995 to 2000, to our knowledge, we examined the regional difference in the annual ESRD incidence in these same 6 years as shown in Table 1. The difference among 11 regions was significant based on ANOVA ($P < 0.0001$). The regional difference in ESRD incidence obtained in the recent 6 years between 1995 and 2000 was highly correlated with that we reported in 17 years between 1982 and 1998 ($r = 0.92$, $N = 11$, $P < 0.0001$) [1].

Usage of antihypertensive drugs and regional differences in ESRD incidence

The sum of antihypertensive drugs (yen per person per year) prescribed from 1995 to 2000 in money basis corrected for population significantly differed among 11 regions across Japan in total antihypertensives, ACE inhibitors, and calcium antagonists ($P < 0.0001$). Linear regression analysis showed, among antihypertensives, only the sum of ACE inhibitors in each region had a negative relationship with the annual incidence of ESRD ($r = -0.40$, $P = 0.0009$) in corresponding regions (Fig. 1) (Table 2).

Other factors correlated with regional differences in ESRD incidence

Neither average age of ESRD patients entering dialysis therapy nor percentage of the population older than 65 years in each region had correlations with the annual incidence of ESRD. However, percentage of old population in each region had significant positive relationships with sums of total antihypertensives ($r = 0.67$, $P < 0.0001$), ACE inhibitors ($r = 0.51$, $P < 0.0001$), and calcium antagonists ($r = 0.77$, $P < 0.0001$) as well as average age of ESRD patients ($r = 0.80$, $P < 0.0001$). Average age of ESRD patients in each region also had

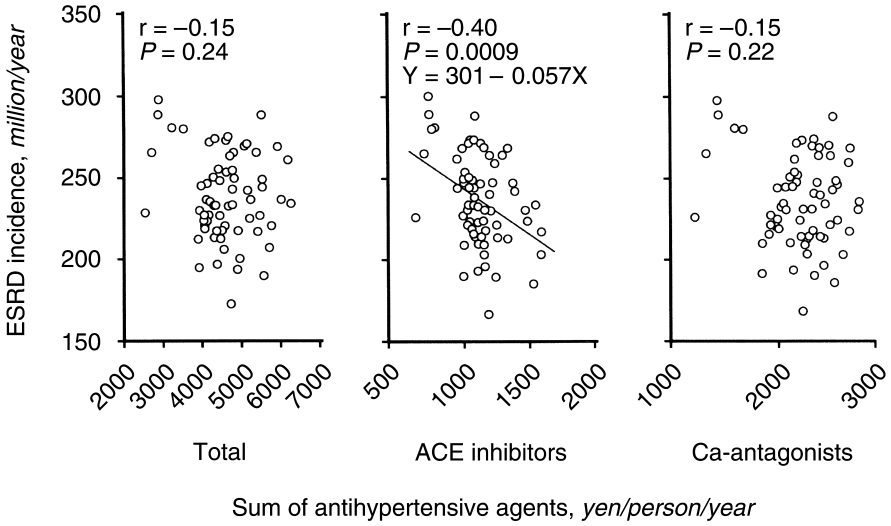

Fig. 1. Relationships of the sums of total antihypertensive drugs, angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists prescribed in money basis corrected for population in each region with the annual incidence of end-stage renal disease (ESRD) in corresponding regions. The number of observations were 66, because the 11 regions were multiplied by 6 years. The sum of antihypertensive drugs was represented in Japanese yen per person per year.

Table 2. Linear and multiple correlations of usage of antihypertensive drugs and other factors with annual end-stage renal disease (ESRD) incidence

$N = 66$	Linear correlation (correlation coefficient)	Multiple regression (standard coefficient)
Multiple correlation coefficient		**0.57 (F = 15.2, $P < 0.0001$)**
Total antihypertensives	−0.15 ($P = 0.24$)	**0.84 (F = 15.7)**
ACE inhibitors	**−0.40 ($P = 0.0009$)**	**−1.13 (F = 28.5)**
Calcium antagonists	−0.15 ($P = 0.22$)	0.10 (F = 0.7)
Age	0.12 ($P = 0.33$)	0.03 (F = 0.1)
Aged population	0.009 ($P = 0.94$)	0.04 (F = 0.1)

ACE is angiotensin-converting enzyme. Significant factors are shown in **bold** figures.

significant positive relationships with sums of money spent on total antihypertensives ($r = 0.64$, $P < 0.0001$), ACE inhibitors ($r = 0.38$, $P = 0.0015$), and calcium antagonists ($r = 0.70$, $P < 0.0001$).

Multiple regression analysis to identify factors independently affecting the regional difference in ESRD incidence

Stepwise forward multiple regression analysis showed that the sum of ACE inhibitors worked as an independently negative factor to reduce the ESRD incidence, while the sum of total antihypertensive drugs as a positive factors to increase it (see Table 2). None of the sum of calcium antagonists, average age of ESRD patients, or percentage of aged population in each region correlated with the annual ESRD incidence in multiple regression analyses.

DISCUSSION

The present study showed a marked regional difference within Japan in the annual incidence of ESRD entering maintenance dialysis therapy even for the recent 6 years between 1995 and 2000, similar to that we previously reported in 17 years between 1982 and 1998 [1]. Once the regional differences in ESRD dynamics have been established, the factors affecting the differences must be elucidated. Since the race is relatively uniform within Japan, the modifiable factors other than genetic may play an important role in creating the regional differences. If we can identify such factors, the strategy to prevent renal failure will be strengthened.

Using an ACE inhibitor is now considered one of the most promising interventions to arrest renal failure [5–10]. Therefore, in this study, we intended to examine the relationships between the regional differences in ESRD dynamics and the prescribed sum of ACE inhibitors. In fact, ACE inhibitors were identified as a significant factor to reduce the incidence of ESRD by both linear and multiple regression analyses. It should be noted here that despite a similar regional distribution as ACE inhibitors, calcium antagonists had no significant relationships with ESRD dynamics, either positively or negatively, in linear and multiple regression analyses. This neutral action of calcium antagonists on renoprotection seemed consistent with other reports [9, 13]. Furthermore, multiple regression analysis showed that in contrast to ACE inhibitors, acting as an independently negative factor, the sum of total antihypertensive drugs worked as an independently positive factor to increase

the ESRD incidence. Since the sum of total antihypertensives may reflect the severity of hypertension, this positive relationship suggests that overall blood pressure level played a significant role in the progression of renal failure. Our findings that ACE inhibitors and total antihypertensives worked in opposite directions with each other in protecting kidneys seemed to characteristically reveal a renoprotective action of the former.

In Japan, captopril was introduced in 1983 as the first ACE inhibitor and enalapril in 1986 as the second. Although we showed in the **Results** section that the regional difference in ESRD incidence obtained in the recent 6 years between 1995 and 2000 was highly correlated with the data we reported in 17 years between 1982 and 1998 ($r = 0.92$, $N = 11$, $P < 0.0001$) [1], we know that the regional difference has changed significantly with time. When the annual ESRD incidence was compared in 5-year periods between the old phase of 1982 to 1986 and the recent phase of 1996 to 2000, the regional difference was significantly influenced by phases (an interaction between regional difference and phases using two-way ANOVA, $P < 0.0001$). Since the ESRD incidence was increased by approximately three times with time in 17 years [1], the recent data (1995 to 2000) strongly influenced the entire data of 17 years, resulting in significant correlation despite clear difference in regional distribution of ESRD incidence between two phases. In addition, the increase in annual ESRD incidence in the above 5-year periods during 14 years from older to recent phases was analyzed in relation with usage of antihypertensives in the recent 5 years (1996 to 2000). Linear regression analysis showed only ACE inhibitors had significant negative correlations with the increase in ESRD incidence (total antihypertensives, $r = -0.17$, $P = 0.21$; ACE inhibitors, $r = -0.31$, $P = 0.020$; and calcium antagonists, $r = -0.24$, $P = 0.077$, $N = 55$). Multiple regression analysis also identified that only ACE inhibitors were the negative factor independently working to suppress the increase in the ESRD incidence (multiple correlation coefficient = 0.31, F = 5.7, $P = 0.02$, $N = 55$; ACE inhibitors, $r = -0.31$, F = 5.7; total antihypertensives, $r = 0.19$, F = 2.1; and calcium antagonists, $r = 0.07$, F = 0.2). These analyses support our findings that ACE inhibitors are one of the major factors determining the regional difference in ESRD dynamics. It remains unproved from our approach, however, whether the introduction of ACE inhibitors has in fact delayed the progression of nephropathy due to lack of enough data for regional differences in ESRD dynamics in the periods before introduction of ACE inhibitors.

On the other hand, it has been documented that long-term treatment is required to fully manifest the renoprotective actions of ACE inhibitors [14]. Therefore, there may be a time lag between the spread of ACE inhibitor consumption and the emergence of its effects on the reduction of ESRD. We repeated analyses using ESRD data in later 3 years (1998 to 2000) and data of antihypertensives in earlier 3 years (1995 to 1997) to examine time-lag effects. Similarly, as whole data in 6 years (1995 to 2000), ACE inhibitors were identified as a significant factor to reduce the incidence of ESRD by both linear and multiple regression analyses ($r = -0.37$, $P = 0.036$, $N = 33$; multiple correlation 0.37, F = 4.8, $P = 0.036$, $r = -0.37$, F = 4.8). Neither total antihypertensives nor calcium antagonists were significantly correlated with ESRD dynamics in the 3-year data. Thus, our data in 3 and 6 years both consistently suggest the renoprotective actions of ACE inhibitors. There might be still other factors to explain for the regional differences in ESRD dynamics such as dietary intake of protein and sodium as well as socioeconomic status. Clearly, much effort will be required to identify such factors, which will clarify the strategies to halt the renal failure progression.

ACE inhibitors have been first proposed to arrest the progression of nephropathy in variety of animal models including diabetic nephropathy [5] and renal ablation models [6]. Large-scale clinical trials also showed that these agents could slow the disease progression in diabetic and nondiabetic nephropathies [7, 9, 14–18]. Now, therefore, ACE inhibitors are recommended in guidelines as compelling drugs for hypertensive patients with renal dysfunction [19, 20]. Our epidemiologic and ecologic data confirm from a different approach that ACE inhibitors are indeed working to arrest renal disease progression in clinical practice.

CONCLUSION

The present study, relating regional differences between ESRD dynamics and usage of antihypertensives in a nationwide population of Japan, on a macro level, confirmed the renal protective effects of ACE inhibitors, established by animal models of progressive nephropathies and large-scale clinical trials.

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